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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99-CV-2668H AJB

DECLARATION OF DR. KARY B. MULLIS IN SUPPORT OF GEN-PROBE INCORPORATED'S MOTION FOR PARTIAL SUMMARY JUDGMENT OF NON-INFRINGEMENT UNDER THE DOCTRINE OF EQUIVALENTS

Date: November 13, 2001
Time: 10:30 a.m.
Place: Courtroom 1

HONORABLE MARILYN L. HUFF

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I, Kary B. Mullis, residing at Newport Beach, California, do hereby declare as follows:

I.

INTRODUCTION

1. I am familiar with nucleic acid amplification methods. Most notably, I conceived a method for specific amplification of nucleic acids in the spring of 1983 while I was employed at Cetus Corporation. This method, the "Polymerase Chain Reaction" method (or "PCR"), rapidly became one of the most widely used and important methods in molecular biology and nucleic acid diagnostics. In 1993, I received the Nobel Prize in Chemistry for the invention of PCR. My education and experience are set forth in my curriculum vitae, attached hereto as Exhibit "A."

2. I have been retained as an expert witness in this lawsuit to render an opinion concerning whether the method of specific amplification used by Gen-Probe is the "equivalent" of the non-specific amplification methods disclosed in United States Patent No. 5,750,338 (the "'338 Patent").

3. As a result of my experience with and knowledge of nucleic acid amplification and nucleic acid diagnostics, I am familiar with the method of specific amplification, Transcription-Mediated Amplification ("TMA"), used by Gen-Probe in its amplified nucleic acid tests.

4. I have reviewed the '338 patent, including its specification and claims. I understand that the '338 patent relates to a method and kit for assaying target polynucleotides incorporating steps of isolating a target nucleic acid from a sample and then amplifying the target nucleic acid.

5. I have reviewed the Court's order granting partial summary judgment in this case on the issue of literal infringement. I understand that the Court has ruled that the term "amplifying" as used in the claims of the '338 patent literally encompasses only *non-specific* amplification methods. I also understand that Vysis did not dispute that TMA products do not use any method of non-specific amplification, and that the Court has therefore ruled that Gen-Probe's TMA method is not literally encompassed by the claims of the '338 patent.

6. It is my understanding that Vysis contends that Gen-Probe's TMA products are covered by the claims of the '338 patent under the judicial doctrine known as the "doctrine of equivalents."

II.

SUMMARY OF OPINION

7. It is my opinion that methods of sequence-specific amplification such as Gen-Probe's TMA method are not the "equivalent" of non-specific amplification methods. It is my opinion that there are substantial differences between Gen-Probe's TMA method and the non-specific amplification methods described and claimed in the '338 patent. Specific amplification methods do not perform substantially the same function in substantially the same way to achieve substantially the same result as non-specific methods of amplification.

III.

NUCLEIC ACID AMPLIFICATION

8. The '338 patent relates generally to methods for use in nucleic acid diagnostic tests, including the use of nucleic acid "probes" to detect the nucleic acids (DNA or RNA) of an infectious organism in a patient sample.

9. It is advantageous for a nucleic acid test to be able to detect an infectious organism in a patient sample even when only small numbers of the organism are present. For example, when screening blood intended for transfusion to detect the presence of viruses such as HIV, it is important to be able to detect as few virus particles as possible in order to prevent the transmission of infection.

10. Scientists have long understood that detection of a small amount of a target organism in a sample by nucleic acid tests requires that the number of "target" nucleic acids be increased to a level that is detectable by nucleic acid probes. The process by which additional copies of nucleic acids are created is commonly referred to as nucleic acid "amplification."

11. Nucleic acid amplification utilizes several naturally occurring enzymes. Enzymes are protein molecules that catalyze biological reactions. These enzymes create copies of nucleic acids in the cells of living organisms (i.e., "*in vivo*") in processes generally called "replication" and "transcription." These enzymes include DNA polymerases and RNA polymerases. Each of these enzymes works by binding to a nucleic acid and producing a complementary copy of its sequence. Each enzyme is named for the reaction it catalyzes. For example, a DNA polymerase catalyzes a

reaction that produces a DNA polymer strand, while an RNA polymerase catalyzes a reaction that produces an RNA polymer strand.

12. Scientists have learned to use enzymes such as nucleic acid polymerases to increase the amount of a DNA or RNA in a laboratory sample up to a billion-fold. Procedures that amplify nucleic acids in a laboratory (i.e., "*in vitro*") are generally performed using DNA polymerases and primers.

13. The primers determine the portion of the nucleic acid of the target organism that will be copied. Primers are short pieces of nucleic acid, which work by binding (or "hybridizing") to a complementary nucleotide sequence of the target organism.[1] Each primer is designed to bind to a portion of the target organism's nucleic acid at the ends of the sequence to be amplified. The

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[1] DNA and RNA are both composed of chains of chemical sub-units called "nucleotides." Each nucleotide has three components: a sugar, a phosphate group, and a "base" containing nitrogen. There are four types of nucleotides in DNA, each of which has a different base: adenine, thymine, guanine, or cytosine (abbreviated A, T, G, and C). These four "bases" form the building blocks of all DNA. The sugar and phosphate groups form the backbone of the DNA molecule, linking together the individual nucleotides that make up the molecule.

The "sequence" of the individual A, T, G, and C nucleotides in a DNA molecule encodes the genetic information that instructs the cell how to make particular proteins. Because DNA sequences determine which proteins a cell will make, it is differences in their DNA sequences that make the cells of one organism differ from the cells of another.

DNA in cells ordinarily occurs in a molecular structure in which two "strands" of DNA are specifically bound to one another. Double-stranded DNA is often depicted as a ladder in which each strand forms one side of the ladder and one half of a rung of the ladder. Each nucleotide's base is chemically bonded to a nucleotide base on the opposite strand to form the rungs of the ladder. In its normal state, the ladder is twisted spirally, forming a three-dimensional "double helix" structure.

In double-stranded DNA, the nucleotides on opposite sides of the ladder are always paired in a precise way. An "A" nucleotide binds only to a "T" nucleotide on the opposite strand, and vice versa. Likewise, a "G" nucleotide binds only to a "C" nucleotide, and vice versa. Each combination of an "A" nucleotide with a "T" nucleotide (or a "C" with a "G") is referred to as a "base pair." The way in which each type of nucleotide binds only to one other type of nucleotide is called "complementary base pairing." As a result of complementary base pairing, the sequence of nucleotides on one strand of a DNA molecule necessarily determines the sequence of nucleotides on the opposite strand.

RNA also consists of a sequence of four bases comprised of four different nucleotides. The four nucleotides contained in RNA are nearly identical to those in DNA. In RNA, thymine (T) is replaced by uracil (U) and the sugar is ribose rather than deoxyribose. Unlike DNA, RNA typically exists as a single strand. However, the nucleotides of RNA have a similar attraction to complementary nucleotides (A binding to U, and C binding to G) and two RNA molecules, or an RNA and a DNA molecule, can form a double helix in which the two strands are joined by complementary base pairing.

site at which a primer binds to a target nucleic acid defines the starting point for DNA synthesis. Following the binding of the primer, the DNA polymerase carries out DNA synthesis beginning at one end of the primer. The newly synthesized DNA is added to, and therefore incorporates, the primer. Generally, practical *in vitro* amplification methods use two primers to produce a copy of the sequence that occurs *between* the two points where the primers bind to the target nucleic acid. Each new DNA strand represents an increase or "amplification" of the specific nucleic acid sequence from which it is copied. Further amplification takes place when the enzymes and primers work in a coordinated way to make additional copies of that specific sequence. In "exponential" amplification methods, such as PCR and TMA, the specific nucleic acid copies made in each round of amplification serve as additional templates for copying in subsequent rounds, so that the process makes "copies of the copies" and billions of copies can be made in a short time.

14. Amplification methods that make RNA copies (as opposed to those making DNA copies, discussed above) generally use an enzyme called "RNA polymerase" or "transcriptase" to make RNA copies from a DNA template. The transcriptase binds to a specific sequence in the DNA, known as a "promoter" and initiates synthesis at that site. Thus, in contrast to DNA polymerases that begin DNA synthesis with a primer, transcriptases use no primer and instead begin synthesis at a particular sequence that is recognized by the enzyme. Different transcriptases recognize different specific promoter sequences at which they begin to make RNA.

15. I consider the level of ordinary skill in the art of molecular biology at the filing date of the '338 patent application to have been that of an individual with a Ph.D. in the biological sciences and two years of postdoctoral experience. Such experience would have allowed the individual to develop skills with the techniques of DNA and RNA isolation and characterization, DNA sequencing methods, and nucleic acid amplification.

III.

SPECIFIC AMPLIFICATION AND NON-SPECIFIC AMPLIFICATION ARE NOT "EQUIVALENT"

16. My understanding is that a method is considered to be an "equivalent" under the doctrine of equivalents only if there are insubstantial differences between the two methods, i.e., only if they perform substantially the same function in substantially the same way to achieve substantially the same result.

17. There are very major and substantial differences between methods of specific amplification and non-specific amplification, and this fact is well known to those of ordinary skill in the art. These two distinct methods of amplification do not perform substantially the same function in substantially the same way to achieve substantially the same result, and this fact is well known to those of ordinary skill in the art.

A. *Specific And Non-Specific Amplification Methods Do Not Perform Substantially The Same Function*

Summary

18. Specific amplification functions to increase exponentially both the ***absolute*** and ***relative*** amount of a particular nucleic acid sequence of interest in a mixture of nucleic acids. In direct contrast, non-specific amplification functions to increase the absolute amount of all nucleic acids in a sample, and does ***not*** increase the relative amount of a particular sequence of interest. This difference is critical with respect to the utility of the two methods. The differences in function of specific amplification and non-specific amplification are well known to persons skilled in the art.

Discussion

19. In order for a procedure to efficiently detect a nucleic acid sequence in the presence of others, it is necessary that the sequence to be detected stand out in some way from the other sequences which are similar (but which are not of interest and therefore must be ignored). Near the end of the procedure the amount of the specific sequence to be detected must exceed, or at least be highly significant, compared to the amount of the background (all the sequences which need to be

ignored). The *relative* amount of the target sequence must be adequate for detection. Where the relative amount of the target sequence is initially inadequate, the relative amount of the sequence can be increased by either diminishing the amount of the background sequences, or increasing the amount of the sequence to be detected or both.

20. The only other consideration in detecting a nucleic acid sequence is that the sequence to be detected, at the end of the procedure, must be present in sufficient *absolute* amounts such that it will register in a significant way in some detection system. For a detection system to register a result there must be some minimum amount of the sequence-bearing molecule present in the sample. In practical terms, because of the limitation of present detection technology, this amount may be much larger than the amount of any particular nucleic acid sequence (e.g., a small amount of hepatitis C virus RNA) that is present in the material of origin, as in human blood. However, in working to increase the absolute amount of a target nucleic acid, there is an upper limit on the total amount of sample that detection methods can process. If one amplifies non-specifically, the amount of the nucleic acid in the entire sample may have been increased to the point that it is impossible to analyze it, even if the amount of the target sequence has been increased to detectable levels. Therefore one must somehow increase the *relative* amount of only the sequence of interest. Specific amplification permits such a process.

21. Sequence-specific amplification methods such as PCR and TMA enable a cyclic chain reaction of biochemical polymerization reactions. Both methods systematically increase the total amount of a specific nucleic acid present and thus the ratio of specific target nucleic acid to non-target background nucleic acid. These methods increase both the absolute and relative amounts of the target sequence.

22. Thus, PCR and other methods of specific amplification are extremely powerful techniques for finding the nucleic acid equivalent of the proverbial "needle in the haystack." When a particular nucleic acid sequence of interest is contained in a mixture of nucleic acids in a clinical sample, specific amplification methods enable a person skilled in the art to exponentially copy the sequence of interest. Specific amplification functions to increase exponentially both the ***absolute*** and ***relative*** amounts of the sequence of interest. Thus, specific amplification methods increase the

copies of the "needle" until there are more copies of the needle than the haystack. This makes it easy to determine whether or not a pathogenic microorganism is hiding among millions of other organisms in a patient sample.

23. In contrast, non-specific amplification is ***not*** a powerful tool for finding a needle in a haystack. Non-specific amplification makes more copies of *everything* -- both the needle and the haystack. Non-specific amplification does not change the relative proportions of the needle and the haystack. When nucleic acids other than the particular sequence of interest are contained in a sample, the other nucleic acids will be multiplied by non-specific amplification. Thus non-specific amplification does not increase the amount of the sequence of interest relative to all other nucleic acids in the sample. Therefore, specific and non-specific amplification methods do not perform substantially the same function. The specific amplification of a certain pre-selected nucleic acid from a sample, which may represent an almost infinitesimally small percentage of the total nucleic acids in that sample, is substantially different from the non-specific amplification of all nucleic acids in the sample.

24. It is true that all nucleic acid amplification techniques have some element of non-specificity. However, when employed by one skilled in the art, methods of sequence-specific amplification, such as TMA and PCR, are extremely specific as compared with amplification using random hexamer primers and non-specific enzymes. The difference in specificity is like the difference between night and day. PCR and TMA are both 1,000,000 times more specific than any non-specific amplification system, and the consequences of this are absolute.

25. I understand that Vysis has previously admitted that Gen-Probe's TMA products do not use any method of "non-specific amplification." The fact that TMA and PCR may result in some very limited amount of amplification of non-target sequences does not render those sequence-specific methods the equivalent of non-specific amplification methods with random hexamer primers and non-specific enzymes, which are deliberately designed to be *totally* non-specific. Although TMA and PCR may generate limited amounts of non-target sequences, these specific amplification methods function to increase exponentially both the ***absolute*** and ***relative***

amount of the sequence of interest, as intended. PCR is useful for detecting biologically significant sequences in clinical laboratories. So is TMA. Non-specific amplification is not.

B. Specific And Non-Specific Amplification Methods Do Not Perform In Substantially The Same Way

Summary

26. Specific amplification is performed with carefully-designed sequence-specific primers that bind to unique nucleic acid sequences in the target organism. In contrast, non-specific amplification is performed with standard or "universal" primers, which bind to any and all nucleic acids present in the sample. These differences between specific amplification and non-specific amplification are well known to persons skilled in the art.

Discussion

27. Paragraph 36 of the Persing report states that the amplification techniques disclosed and claimed in the '338 patent "perform in substantially the same way" as TMA. This statement is false. It is well known to those skilled in the art that the techniques of specific amplification are substantially different from the techniques of non-specific amplification.

28. The enzymes and primers used in amplification processes can each be specific or non-specific. The primers used in *specific* amplification procedures are carefully selected by scientists and are generally designed to bind to specific, unique sequences in a DNA or RNA molecule. Such primers are referred to as "specific" or "sequence-specific" primers. Perhaps the most well-known method of specific amplification is the PCR method, which I invented and for which I received the Nobel Prize. The PCR method uses carefully selected sequence-specific primers to amplify a particular nucleic acid sequence. This specific sequence may be contained within a larger sequence or a large collection of sequences; the PCR method isolates a specific portion of the sequences present to be selectively amplified.

29. Designing specific primers requires some knowledge of the intended target sequence and often requires laboratory testing to determine if the sequence-specific primers, in fact, function in a sequence-specific manner to amplify the intended target sequence. The judicious choice of oligonucleotide primers is a critical element in determining the performance of specific

amplification methods. Several considerations come into play when designing specific primers: oligonucleotide length; oligonucleotide melting temperature; sequence composition; physical characteristics; primer-primer interactions; length of the amplified target; location on the target sequence; and whether or not closely related non-target sequences might be present. It is common for scientists to design, test and then redesign and retest sequence-specific primers to achieve effective sequence-specific amplification of the desired target sequence.

30. In contrast to sequence-specific primers that are designed to amplify a particular nucleic acid target, "universal" or "random" primers are used when a scientist desires to amplify *any* and *all* nucleic acid sequences that are present in a sample. Random primers are mixtures of primers that cumulatively contain thousands of random nucleotide sequences. For example, random primers are often collections of short DNA fragments, averaging about 6 nucleotides in length, where each primer in the collection can contain any permutation of the four bases (A, T, G, and C) that make up DNA. Such short sequences are called "random hexamers." Random hexamer primers can bind to complementary hexamer sequences that occur frequently within virtually all nucleic acids. Thus, random primers will bind at multiple points along any nucleic acid sequence and initiate copying from all positions to which they bind, copying any nucleic acids that may be present in the sample. Using random primers, a nucleic acid sequence is replicated as a set of smaller fragments, each beginning with the sequence of its initiating random primer. Random hexamer primers have been commercially available since the 1970's. By using "universal" or "random" primers in an amplification process, it is possible to avoid the labor and cost needed to design, test and develop specific primers for each target nucleic acid. In contrast to the careful selection steps used to identify specific primers, the use of non-specific random hexamer primers for non-specific amplification requires no choice or selection. The trade-off for the ease and reduced cost in using random primers is that the amplification process will not specifically amplify the sequence of interest, and instead will amplify any nucleic acid present in the reaction mixture (including sequences in the sample that are not of interest).

31. Enzymes used in amplification methods can be specific or non-specific: Examples 4 and 5 of the '338 patent refer to such enzymes, e.g., "RNA polymerases that lack transcriptional specificity," including "*E. coli* RNA polymerase lacking sigma subunit, i.e., core enzyme."

32. In amplification processes, sequence-specific primers and enzymes such as those used in TMA play a role substantially different from primers and enzymes that lack specificity. This fact is well known to those of ordinary skill in the art. "Specific" primers and enzymes can function together to amplify a target nucleic acid only if the specific sequence of interest bound by the primer and/or recognized by the enzyme is present in the sample. In fact, a number of diagnostic assays simply determine whether or not PCR amplification has occurred, or whether the specific primers have been incorporated into larger size products, to test for the presence of a particular nucleic acid sequence in a clinical sample.

33. By contrast, non-specific primers and enzymes will amplify *any* and *all* sequences present in the sample. The random primers will bind to all of the sequences in the sample and non-specific replication enzymes will catalyze DNA synthesis at points throughout the entire lengths of the nucleic acid molecules present without regard to sequence. In this case, the presence of amplification, or the incorporation of the primers into larger size products, is not diagnostic of the presence of a particular nucleic acid sequence in the sample.

34. I am familiar with Gen-Probe's TMA method of sequence-specific amplification. TMA makes both RNA and DNA. RNA is made at specific promoter sites, created by bi-functional primers that bind to a specific sequence and insert the promoter at that location. DNA is made at sites to which primers bound. TMA achieves amplification using sequence-specific primers, specific promoters, and specific enzymes that initiate copying at those primers and promoters. The TMA process will only amplify nucleic acid captured from a sample if the primers find and bind to their respective specific target sequences.

35. One of the primers used in Gen-Probe's methods also includes a specific "promoter" sequence that is recognized by a specific enzyme (an RNA polymerase that binds specifically to that promoter sequence) to produce many RNA copies by transcription initiating at that promoter sequence. A functional "T7 promoter" is formed in the course of the TMA process if, and only if,

(1) the primer finds and binds to its complementary target sequence in the captured target molecule so that the target sequence is copied by reverse transcriptase and (2) the second primer binds to the newly synthesized DNA and DNA polymerase makes the complementary DNA strand. If this double-stranded, and hence functional, T7 promoter *is* formed as a result of these *two* primer binding and extension processes, then the T7 RNA polymerase used in Gen-Probe's Blood Screening Assay will amplify the sequence attached to the T7 promoter sequence. The T7 RNA polymerase does not amplify other sequences present in the sample because they are not attached to a T7 promoter sequence. Thus, in TMA the T7 polymerase enzyme *specifically* recognizes the T7 promoter sequence, which has been *specifically* attached to the target sequence by the binding of *specific* primers, and the T7 polymerase *specifically* amplifies only that sequence.

36. For the reasons set forth above, specific and non-specific amplification methods do not perform in substantially the same way.

C. Specific And Non-Specific Amplification Methods Do Not Achieve Substantially The Same Result

37. As discussed above, the function and mechanisms of specific amplification are substantially different than those of non-specific amplification. Accordingly, the results achieved by specific amplification are substantially different than the results achieved by non-specific amplification.

38. First, specific amplification methods result in the increase in a particular nucleic acid sequence, in both ***absolute*** and ***relative*** terms. Non-specific amplification does not achieve an increase in the amount of a particular nucleic acid ***relative*** to other nucleic acids present in the sample.

39. Second, specific amplification methods commonly achieve ***exponential*** amplification of the target sequence, as compared with linear amplification. Extensive, sustainable exponential amplification is a hallmark of specific amplification methods such as PCR and TMA. For example, in every cycle of PCR, because the copies made in a prior round are used as templates in the succeeding round, the number of copies of target sequence increases by a factor of two. (Non-target sequences are unaffected or randomly destroyed.). The amplification process is

what is referred to mathematically as logarithmic or exponential, which means that after thirty cycles of PCR the number of copies of the target sequence has increased by 2 to the thirtieth power (2^{30}), or by a billion. The use of "billion" here should not be interpreted as hyperbole. Two raised to the thirtieth power (thirty is a typical number of cycles in a PCR reaction) is actually 1,073,741,824. The physical process of PCR, properly performed, follows the mathematical prediction precisely. It was amazing to every DNA chemist when it was first introduced, not only for what it could accomplish, but also for the simplicity of its principle and practice. It is not surprising that in addition to leading to dozens of patents, and a Nobel Prize, it resulted in revolutionary changes in the methods, capabilities and even the lexicon of molecular biology. "Polymerase chain reaction" also entered the English language, as catalogued in Merriam Webster, and the common vernacular as "PCR." Specific amplification does not represent a minor or insubstantial change from non-specific amplification.

40. In contrast, the non-specific amplification methods of Examples 4 and 5 of the '338 patent admittedly achieve only linear amplification, not exponential amplification. Because random primers bind at various places along the nucleic acids present in the sample, the products of amplification are fragmented. If these products are then subjected to another round of non-specific amplification, the newly-made products are smaller still. Multiple rounds of non-specific amplification thus diminish rapidly in efficiency whereas multiple rounds of specific amplification produce extraordinarily large amounts of full-size nucleic acids in very short periods of time.

41. Third, non-specific amplification using random hexamers produces fragmented nucleic acids, each of which contains the random sequences present in the primers. The amplified nucleic acid is thus heterogeneous, with undefined composition. Such nucleic acid is unsuitable for most of the purposes for which specifically-amplified nucleic acids -- highly homogeneous, with known composition -- are employed.

42. Specific amplification is entirely different from non-specific amplification. Dropping the word "specific" from "specific amplification" has astronomical consequences. One simply cannot make a billion copies non-specifically of every nucleic acid in a particular clinical sample. There couldn't be enough nucleic acid starting materials (the monomers) put into the tube,

there are not enough molecules of enzyme to do the transformations, and even if you could and there were, there wouldn't be enough room for the amplified products in the tube. "Specific amplification" of a single sequence or a small set of related sequences *is* possible and *is* very useful. It was spectacular in 1983 when it was first performed and it is still spectacular today. It's not the same as "non-specific amplification" methods -- which no one outside of a small circle has ever heard about -- in the context of useful techniques of *in vitro* diagnostics. Certainly no one is actually using non-specific amplification today in commercial diagnostic tests: There is no reasonable way to equate or even compare "non-specific amplification of nucleic acids" to "specific amplification of nucleic acids."

D. Non-Specific Amplification Methods Cannot be Substituted for Specific Amplification Methods

43. Those skilled in the art do not believe that they can use non-specific amplification to achieve the same results as specific amplification. Those skilled in the art recognize that use of random primers, if it results in amplification, will result in amplification of all nucleic acids that are present in the sample, not just the specific sequence that a scientist is interested in. As a consequence of this fact, persons of ordinary skill in the art have long recognized the fundamental and significant differences that exist between specific and non-specific amplification techniques and the lack of equivalence between those nucleic amplification techniques.

44. Due to the significant differences between amplification of specific sequences and the amplification of random sequences, non-specific amplification techniques cannot be substituted in place of specific amplification methods, such as TMA. Non-specific amplification techniques could not be used in place of specific amplification to detect the presence of minute quantities of infectious organisms in clinical samples.

45. In part, one would know to avoid the use of non-specific amplification techniques as a result of the critical need to enhance the sensitivity of such assays. Because non-specific amplification techniques would amplify all nucleic acids in any given sample, they would not provide the degree of sensitivity necessary to detect minute quantities of infectious organisms in a sample. Sensitivity of non-specific amplification methods is limited because those methods lack

selectivity. One cannot make a billion copies of a million sequences in this lifetime without using a 55-gallon drum, and one cannot inject the contents of a 55-gallon drum into a detection system.

V.

SPECIFIC AMPLIFICATION METHODS ARE EXCLUDED FROM THE PATENT

46. As the Court has ruled, a person of ordinary skill in the art in December 1987, reading the '338 patent specification, would understand the term "amplifying" in the claims to mean using the non-specific amplification methods such as those described and illustrated in the patent. In the '338 patent, the inventors teach that a benefit of their invention is that it *eliminates* the need to design and prepare specific primers for each test and/or the need to use specific enzymes (col. 30, ll. 30-40). It is my opinion that a person skilled in the art would conclude that amplification with sequence-specific primers and enzymes, such as those used in TMA, is intentionally excluded from the scope of the claims of the '338 patent.

47. As of the filing date, PCR was the most commonly used sequence-specific method of amplification known in the art. Although the filing date of the '338 patent was two years after PCR was publicly disclosed, the patent does not describe or teach combining target capture with PCR, or any other amplification methods that use specific primers or enzymes. Although the '338 inventors could have included an example in the patent that combined target capture and sequence-specific amplification (such as PCR), the inventors instead described a method to *avoid* using sequence-specific primers and enzymes. (However, that would be inconsistent with the benefits asserted for the invention, i.e., that it employs non-specific enzymes and primers for amplification.)

VI.

CONCLUSION

48. For the reasons set forth above, one of ordinary skill in the art would conclude that there are substantial differences between Gen-Probe's TMA method and the non-specific amplification methods described and claimed in the '338 patent. Sequence-specific amplification methods such as TMA do not perform substantially the same function in substantially the same way to achieve substantially the same result as non-specific methods of amplification.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct and that this declaration is executed at Newport Beach, California on September 26, 2001.

Kary B. Mullis